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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,522	11/21/2001	Choy-Pik Chiu	097/002	3556

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,522	CHIU ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/05 has been entered.

Applicants elected **without traverse** in the amendment filed on 4/7/03 the following species: (a) the first cell population has characteristics of mesenchymal stem cells; (b) the first cell population expresses CD90; and (c) the second cell population comprises cardiomyocytes or their lineage-restricted precursors.

Amended claims 1-20 are pending in the present application, and they are examined on the merits herein with the aforementioned elected species.

Response to a request for rejoinder

Applicants request for rejoinder of all species because no prior art has been identified to anticipate claim 1.

Although no prior art has been identified to anticipate claim 1, the generic claims with the elected species (e.g., mesenchmal stem cells or first cell population expressing CD90 and cardiomyocytes as the second cell population) are still rejected under 35 U.S.C. 112, first paragraph, for the reasons discussed below. Therefore, there is no requirement for the examiner to search and determine patentablility for all other pending

species which would be unduly burdensome for the examiner. Furthermore, Applicants have elected the aforementioned species **without traverse** in the amendment filed on 4/7/03.

Claim Objections

Claim 1 is objected to because of the lack of the article - - a - - in from of the term "subject" on line 6 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to **make and/or** use the invention. ***This is a modified rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the instant claims are drawn to a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders a subject to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells and is MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same cell populations for use in regenerative medicine as well as methods for reconstituting cellular function or preparing a subject for therapy to reconstitute their cellular function using the same.

The instant specification describes in general that human ES cells can be differentiated into tolerizing cells by forming embryoid bodies or by direct differentiation in a suitable culture environment with suitable medium, and that relevant markers for mesenchymal stem cells are: CTLA-4, SH2+, SH3+, CD29+, CD44+, CD71+, CD90+, CD106+, CD14-, CD34-, CD45-. Additionally, the present disclosure states that scientists at Geron Corporation have discovered that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors.

However, the instant specification is not enabled for the presently claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims encompass a combination of pharmaceutical compounds comprising: (a) a first cell population that has been differentiated from human pluripotent stem (hPS) cells into a phenotype that renders any subject (both human and non-human subjects) to whom it is administered immunotolerant to a second cell population that is differentiated from hPS cells, not necessarily derived from the same hPS cells, and is MHC compatible with the first cell population, wherein the first cell population has characteristics of mesenchymal stem cells or one that expresses CD90 cell marker and the second cell population comprises cardiomyocytes; a method for preparing the same cell populations for therapeutic use in regenerative medicine as well as methods for reconstituting cardiomyocyte function or preparing a subject for therapy to reconstitute cardiomyocyte function using the same by administering the first and second cell populationd by any route of delivery into the subject.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application (11/22/2000), little was known about tolerance induction and/or cardiac repair or regeneration for human allograft patients using a combination of elected cell populations differentiated from human pluripotent stem cells (Waldmann, Nature Med. 5:1245-1248, 1999; IDS; Sussman, Nature 410:640-641, 2001). Kaufman et al. (PNAS 98:10716-10721, 2001) state "**If** human ES cell-derived HSCs can be used to create hematopoietic chimerism in a patient, that patient should be tolerant to other tissues derived from the same ES cells and would not require any continuous immunosuppressive treatment", and "The clinical promise of human ES cell-base

therapies is great; however, because these therapies will be entirely novel, serious concerns about safety and efficacy will need to be addressed before human clinical trials can be initiated" (page 10721, col. 1). Furthermore, in a post-filing art (Nature Med. 8:171-177, 2002; IDS), Fandrich et al. also note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, let alone in any other non-human subjects (page 176, col. 2, second full paragraph). Additionally, with respect to the immunobiology and use of human mesenchymal stem cells, even four years after the effective filing date of the present application (11/22/2000), Le Blanc et al. (Biology of Blood and Marrow Transplantation 11:321-334, 2005) still state "Many questions regarding MSCs can not be answered today. Most of what is known about MSCs is derived from *in vitro* experiments. When administered *in vivo*, MSCs have been difficult or almost impossible to detect. There is very limited experience with MSCs administered to humans" (page 328, right column, top of second paragraph).

With respect to the utilization of cardiomyocytes in cardiac muscle repair and/or regeneration, Grounds et al. (J. Histochem. Cytochem. 50:589-610, 2002) state "Although some experiments in animal models report successful engraftment and maturation of embryonic cardiomyocytes in normal and injured hearts ...., other studies show that most of the donor cardiomyocytes (engrafted into mature rat hearts after infarction) retained their embryonic phenotype and did not form junctions with mature heart cells by 4 weeks...Although neonatal donor cells could form junctions with host myocardium, there was massive initial death of donor cells and at later times the grafts

were often isolated by scar tissue...This problem is a direct result of the inflammation and scarring after infarction, and it may be that use of cardiomyocyte transplantation therapy could be more effectively developed to address functional improvement in myopathic heart diseases" (page 602, col. 2, first paragraph). Grounds et al. further teach that although it has been shown in tissue culture that human ES cells can also differentiate into cardiomyocytes, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice (<10% compared with >80% of murine ES cells; a median of 11 days for differentiation compared with 2 days for murine cells), and that the use of embryonic stem cells as a source of cardiomyocytes is an attractive therapeutic possibility that needs to be fully explored (page 604, col. 2 under the section titled "Embryonic stem cells").

(3) The amount of direction or guidance provided. Apart from the general prophetic disclosure that human ES cells can be differentiated into tolerizing cells including mesenchymal stem cells, and that it is possible to differentiate hPS cells into a highly enriched population comprising cardiomyocytes or cardiomyocyte precursors, the instant specification fails to provide any specific guidance including the relevant *in vitro* and *in vivo* examples, for a skilled artisan on how to obtain and use any effective amount of mesenchemal stem cells derived from hPS cells with the desired property (e.g., rendering any treated human or non-human subject immunotolerant to the second cell population) together with any effective amount of cardiomyocytes differentiated from hPS cells to attain any therapeutic effects contemplated by Applicants (e.g., repair and/or regeneration and/or reconstituting cardiac function in any treated subject). It is

unclear under which specific conditions and/or parameters, an effective amount of tolerizing mesenchymal stem cells or tolerizing cells expressing CD90 or cardiomyocytses could be obtained via the differentiation of hPS cells in culture that could be used to obtain the contemplated therapeutic effects. Particularly, human ES cells are known to be very inefficient to differentiate into cardiomyocytes even in 2002 (Grounds et al.; Cited above). In a post-filing art, Xu et al. (Cir. Res. 91:501-508, 2002) also state "The difference in the efficiency of cardiomyocytes differentiation may reflect differences in culture conditions of the undifferentiated hES cells, methods used for the dissociation of hES cells to generate Ebs, the length of EB suspension culture, and/or the quality of serum used for differentiation" (page 506, col. 2, first full paragraph). There is no evidence of record indicating that the combined cell populations differentiated from hPS cells could survive in an allogenic host environment for a sufficient time period to yield the contemplated therapeutic effects, let alone in any non-human subject. Fandrich et al. note that the potential for mouse or human embryonic stem cells or their progenitor cells to survive in an allogenic host environment has not been reported, even in 2002, let alone at the effective filing date (11/22/2000) of the present application (page 176, col. 2, second full paragraph). Grinnemo et al. (The Journal of Thoraic and Cardiovascular Surgery 127:1293-1300, 2004) report that adult human mesenchymal stem cells are rejected in a xenogenic model even though they did not induce xenoreactivity *in vitro*. Moreover, in a related study Bachar-Lustig et al. (Blood 94:3212-3221, 1999; IDS) note that it might be difficult to harvest sufficient Sca-1+Lin- bone marrow progenitor cells in humans at megadoses required for overcoming

major transplantation barriers (see abstract). The instant specification also fails to provide any guidance demonstrating that any route of administration of the cardiomyocytes at any site in the treated subject would result in the homing of the delivered differentiated second cell population in an effective amount to the heart to yield the desired therapeutic effects contemplated by Applicants. It is also unclear whether the administered cardiomyocytes are capable of establishing the architecture needed to restore or reconstitute any cardiac function, or whether the administered cardiomyocytes differentiated from hPS cells are capable of electrical coupling with treated host cardiomyocytes and subsequent generating an active mechanical force in the treated subject and/or for how long they can survive to yield the desired therapeutic effects contemplated by Applicants.

Since the prior art at the effective filing date of the present application does not provide guidance for the issues discussed above, it is incumbent upon the present application to do so. Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art particularly the art on tolerance induction and/or cardiac repair or regeneration for human allograft patients using cell populations differentiated from human pluripotent stem cells, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **make and use** the presently claimed invention.

Response to Arguments

Applicants' new arguments related to the above rejection in the Amendment filed on 4/1/05 (pages 6-10) have been fully considered, but they are not found persuasive for the reasons discussed below.

1. With respect to the issue of the properties of ES-derived cardiomyocytes, Applicants argue that there is no requirement to place in the specification aspects of a method that can be determined by routine experimentation, or that is known in the art through other published information. Applicants further argue that methods for making cardiomyocytes in the manner of Xu et al. (Cir. Res. 91(6): 501-508, 2002) had already been disclosed in considerable detail at the time of filing of the present application (9/10/01) as evidenced by the filing of USSN 60/305,087, filed July 12, 2001; USSN 60/322,695, filed September 10, 2001, which are priority documents for US application 10/193,884. Additionally, the information presented on the bottom paragraph of page 11 of this application provides a summary of some of the features of a particular method, which will inspire the reader to fill in further details from what is already available to the public, including but not limited to USSN 60/305,087 and 60/322,695.

Firstly, it is noted that a method for making or enriching cardiomyocytes from the differentiation of human pluripotent stem cells is not a routine experimentation. Xu et al. (Cir. Res. 91:501-508, 2002) state "The difference in the efficiency of cardiomyocytes differentiation may reflect differences in culture conditions of the undifferentiated hES cells, methods used for the dissociation of hES cells to generate Ebs, the length of EB suspension culture, and/or the quality of serum used for differentiation". Additionally,

even in 2002, Grounds et al. teach that although it has been shown in tissue culture that human ES cells can also differentiate into cardiomyocytes, human ES cells have a very low efficiency of conversion into cardiomyocytes compared with those of mice (<10% compared with >80% of murine ES cells; a median of 11 days for differentiation compared with 2 days for murine cells), and that the use of embryonic stem cells as a source of cardiomyocytes is an attractive therapeutic possibility that needs to be fully explored (page 604, col. 2 under the section titled "Embryonic stem cells").

Secondly, the disclosures of USSN 60/305,087 and 60/322,695 that are the priority documents of US application 10/193,884, filed on July 12, 2002, are not readily available to the public at the filing date of the present application (11/21/2001). How can they be when the US application 10/193,884 was filed on July 12, 2002? Additionally, Grounds et al were not even aware of these disclosures in their review article published in 2002.

Thirdly, the information presented on the bottom paragraph of page 11 of this application does not teach any critical parameters or conditions required for the making and/or enriching cardiomyocytes from the differentiation of human pluripotent stem cells in any effective amount to yield any therapeutic effect in any subject as contemplated by Applicants.

Therefore, in light of the overall state of the prior art as discussed above coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the presently claimed invention. It is further noted that the specification must teach all the critical

elements that are essential for the practice of the claimed invention, and that it can not rely on the information that may or may not be available in the prior art.

2. The Declaration under 37 CFR 1.132 filed 4/1/05 is also insufficient to overcome the rejection of claims 1-20 based upon insufficiency of disclosure under 35 U.S.C. 112, First paragraph, as set forth above because: the merely disclosure that a cardiomyocyte obtained using 5-azacytodine as described in the present application has the same markers and functional characteristics as the cells used in the animal model experiments described in Dr. Joseph Gold's earlier Declaration is not sufficient to overcome the various issues already set forth in the above rejection. For example, at the filing date of the present application, a skilled artisan would not be able to enrich sufficient levels of functional cardiomyocytes from human pluripotent stem cells and in combination with an effective amount of toleragenic mesenchymal stem cells to yield therapeutic effects in any treated subject. The issue is not a simple question whether a human pluripotent stem cell is capable of differentiating into a cardiomyocyte. As already noted previously, the instant disclosure fails to provide any specific guidance including the relevant *in vitro* and *in vivo* examples, for a skilled artisan on how to obtain and use an effective amount of mesenchemal stem cells derived from hPS cells with the desired property (e.g., rendering any treated human or non-human subject immunotolerant to the second cell population) together with an effective amount of cardiomyocytes differentiated from hPS cells to attain any therapeutic effects in any subject as claimed.

3. With respect to the issue of the properties of ES-derived mesenchymal stem cells, Applicants argue that mesenchymal cells are referred to at several places in the specification as an alternative species of toleragenic cells, and that mesenchymal cells have a fibroblast-like appearance. Applicants further refer the examiner to WO 01/51616 filed on July 19, 2001 for the making of HEF1 line which cells have phenotypic characteristics of mesenchymal cells. Applicants also referred the examiner to the post-filing art of Xu et al. (Stem Cells 22:972-980, 2004) to the making of HEF1-hTERT cells. Applicants further argue that there is no evidence suggesting that telomerizing the HEF1 cells imbued them with properties relevant to toleragenicity that were different from any other mesenchymal cells made from hES cells by standard procedures. Once again, Applicants argue that USSN 60/303,732, filed on July 6, 2001, which is the priority document of US application 10/189,276 that describes detailed methods for making mesenchymal cells from hES cells, is already available to the public as of the filing date of the present application.

Please note that WO 01/51616 filed on July 19, 2001 disclosed the making of HEF1 cells that have phenotypic characteristics of mesenchymal cells to be used to support hES cells in feeder-free culture (see at least example 12). Nowhere in the WO 01/51616 document that one can find a teaching or a suggestion indicating that the HEF1 cells are similar to human mesenchymal stem cells (the elected species, and not simply mesenchymal cells) and/or that HEF1 cells have toleragenic properties in any host. Not until in the article of Xu et al., published in 2004, were HEF1-hTERT cells

characterized and taught to be similar to hMSCs in expressing cell surface markers CD29, CD44, CD71 and CD90 at similar levels to hMSCs (page 977, right column, first paragraph). It is interesting to note that Xu et al also state that "telomerase expression in hMSCs has been shown to enhance their osteogenic potential" (page 978, left column, middle of first paragraph), indicating that the transfected hMSCs cells are not the same as the non-transfected hMSCs.

It is also noted that the disclosure of USSN 60/303,732 which is a priority document of US application 10/189,276 filed on July 03, 2002 was not available to the public as of the filing date of this application which is 11/21/2001. Once again, nowhere in the USSN 60/303,732 document that one can find a teaching or a suggestion indicating that the HEF1 cells are similar to human mesenchymal stem cells (the elected species, and not simply mesenchymal cells) and/or that HEF1 cells have toleragenic properties in any host.

Therefore at the filing date of the present application (11/21/01), a skilled artisan would have no reason to pick and choose specifically the conditions of making HEF1 cells as conditions for differentiating human pluripotent stem cells into human mesenchymal stem cells that have toleragenic properties. Moreover, it should be noted that the specification must teach all the critical elements that are essential for the practice of the claimed invention, and that it can not rely on the information that may be floating somewhere in the prior art.

4. Applicants further rely on two recent scientific publications to provide additional evidence in support of the presently claimed invention, namely the findings of Sasaki et al. (Transplantation 79:32-37, 2005) that showed long-term hematopoietic microchimerism from cynomolgus monkey ES cells after *in vitro* differentiation to mesodermal cells; and the findings of Colson et al. (J. Immunol. 173:5827-5834, 2004) that showed the establishment of xenogeneic chimerism in mice using rat bone marrow cells, and the induced chimerism promoted cardiac xenograft engraftment in an allotype-specific manner. Applicants argue that these recent results showed that ES-derived cells successfully create chimerism *in vivo* and this in turn promotes tissue-specific tolerance which improves engraftment of heart tissue in an allotype-specific fashion. Similarly, if the same hES cell line is made into toleragenic cells and cardiomyocytes, the first cell population could be used to promote engraftment of the second cell population in the same fashion.

It is noted that none of these post-filing arts teaches the attainment of any therapeutic result in any subject from the use of a combination of a mesenchymal stem cell population and a cardiomyocyte cell population that are differentiated from human pluripotent stem cells of the presently claimed invention. Nor does the instant specification teach the specific materials and the specific method steps that are taught by Sasaki et al. and Colson et al. in order to obtain their results. It is also noted that that the breadth of the presently claimed invention is not limited to the attainment of therapeutic effects as a result of an engraftment of cardiac allografts in a subject that has been made tolerant to cells bearing alloantigens from the administration of

mesenchymal stem cell population differentiated from human pluripotent stem cells. Furthermore, the statement "if the same hES cell line is made into toleragenic cells and cardiomyocytes, the first cell population could be used to promote engraftment of the second cell population in the same fashion" is simply Applicants' opinion and that it is not factual evidence.

Accordingly, amended claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth above.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER